

## ORIGINAL ARTICLE

## Crystalline plasma cell inclusions in helicobacter-associated gastritis

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**Background:** Crystalline cytoplasmic inclusions are well documented in B cell lymphomas but have rarely been described in reactive plasmacytic infiltrates.

**Aim:** Three cases of *Helicobacter*-associated gastritis are described in which plasma cells focally contained rhomboid and needle-shaped crystalline inclusions.

**Methods:** Crystalline inclusions were identified in the gastric biopsy specimens from three patients undergoing routine upper gastrointestinal endoscopy. The cells were characterised immunohistochemically using the following antisera: cytokeratin, leucocyte common antigen, desmin, CD20, CD68, CD79a, CD138, immunoglobulin (Ig)G, IgA and IgM heavy chains, and  $\kappa$  and  $\lambda$  Ig light chains. Clinical follow-up data were obtained.

**Results:** All biopsies showed a *Helicobacter*-associated active chronic gastritis. Variable numbers of plasma cells with intracytoplasmic crystalline inclusions in the superficial lamina propria were seen. The crystals were not stained with any of the antisera tested, but the cells containing the crystals expressed CD79a and CD138 and, in the two assessable cases, showed IgA and  $\lambda$  light chain immunoreactivity. The more numerous morphologically normal plasma cells in each patient were polytypic, and there were no histological features to suggest lymphoma. Crystals were not identified in the plasma cells in mucosal biopsy specimens from other sites in any of the patients.

**Conclusions:** Crystalline inclusions in plasma cells can occur in association with *Helicobacter* gastritis. Although light chain restriction was shown in two patients, the overall histological and clinical findings indicated a reactive process. The presence of plasma cell crystals in isolation should not be considered to be diagnostic of lymphoma.

Crystalline inclusions in the cytoplasm of lymphoid cells are an uncommon but well-documented finding in B cell lymphoproliferative disorders, including plasmacytoma, multiple myeloma, chronic lymphocytic leukaemia, lympho-plasmacytic lymphoma, mucosa-associated lymphoid tissue lymphomas and, rarely, high-grade lymphomas.<sup>1–5</sup> The crystals have variable light microscopic appearances and may exhibit rectangular, elongated, needle-shaped or rhomboid morphology. Electron microscopy typically shows crystal localisation in the rough endoplasmic reticulum consistent with synthesised but unreleased immunoglobulin. The demonstration of heavy chain or light chain immunoreactivity further supports the origin of the crystals from aggregated immunoglobulin components. However, the crystals may not be immunoreactive, or special techniques such as immunoelectron microscopy may be required to show specific labelling.<sup>6</sup> Although the crystals usually accumulate in plasma cells, they can also be seen in extracellular locations or in phagocytic histiocytes. In the second situation (crystal-storing histiocytosis), the dominant histiocytic component of the cellular infiltrate may mask the underlying lymphoproliferative disorder.<sup>7–8</sup>

Some authors have noted that intracytoplasmic crystals may also be seen in reactive plasma cell infiltrates,<sup>1–9</sup> but this seems to be a very rare event and few such cases have been documented in detail.<sup>7–10</sup> To our knowledge, crystalline inclusions have been described only once previously in a patient with gastritis,<sup>11</sup> and in that case the plasma cells predominantly showed rounded eosinophilic cytoplasmic inclusions (Russell bodies). In this report, we describe rhomboid and needle-shaped crystalline plasma cell inclusions in three patients with *Helicobacter*-associated gastritis.

## METHODS

Intracytoplasmic crystalline inclusions were identified in the gastric biopsy specimens of three patients undergoing routine gastrointestinal endoscopy because of symptomatic dyspepsia, dysphagia and/or diarrhoea. The patients were identified by one of the authors (CJRS) over a 24-month period in which about 2500 gastric biopsy specimens were examined. At endoscopy, two patients had antral gastritis or erosions, whereas oesophagitis was present in the remaining patient. None of the patients had endoscopic features of malignancy and there was no history of lymphoma or multiple myeloma. Between one and four antral biopsies were performed in each patient and concurrent biopsies were also carried out on the duodenum, colon and rectum (case 1), duodenum, ileum and rectum (case 2) and the oesophagus (case 3).

All biopsy specimens were fixed in 10% buffered formalin and processed in paraffin wax. Sections 4  $\mu$ m thick were stained initially with haematoxylin and eosin for routine diagnostic purposes and Cresyl Violet for identification of *Helicobacter pylori* organisms. After identification of the crystals, additional sections were stained with Sirius Red and periodic acid-Schiff diastase. Immunohistochemical studies were also carried out using the following antisera (dilutions in parentheses): cytokeratin (AE1/AE3 clone, 1/100), desmin (1/200), CD20 (1/800), CD68 (1/300), CD79a (1/300),  $\kappa$  and  $\lambda$  immunoglobulin (Ig) light chains (both 1/60 000), IgA (1/300), IgG (1/200) and IgM (1/200). All antisera were obtained from Dako (NSW 2019, Australia). All staining batches included appropriate positive and negative controls.

## RESULTS

Table 1 summarises the clinical and pathological findings.

**Table 1** Clinical, histological and immunohistochemical findings in three patients with gastric plasma cell crystals

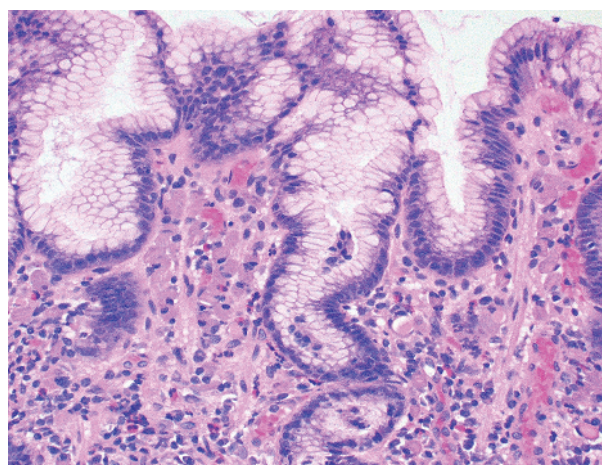
	Age, sex	Symptoms/endoscopy	Gastric biopsy findings	PCC	IHC in PCC	Other findings	Follow-up
Case 1	82, M	Dyspepsia, antral gastritis	Moderate acute and chronic gastritis. HP present	Focal, up to 32/HPF	IgA $\lambda$	No PCC in duodenal, colonic or rectal biopsies No paraprotein on serum electrophoresis	Died of unrelated causes 4 months after biopsy
Case 2	81, M	Dysphagia, oesophagitis	Mild acute and chronic gastritis. HP present	Focal, up to 2/HPF	Insufficient PCC for assessment	No PCC in duodenal, ileal or rectal biopsies	No gastric symptoms 14 months after biopsy
Case 3	52, F	Diarrhoea, oesophagitis, antral erosion	Moderate acute and chronic gastritis. HP present	Focal, up to 5/HPF	IgA $\lambda$	No PCC in oesophageal biopsies	No gastric symptoms 6 months after biopsy History of hypertension and hypothyroidism

F, female; HP, *Helicobacter pylori*; HPF, high-power field ( $\times 400$  magnification); IgA, immunoglobulin A; IHC, immunohistochemistry; M, male; PCC, plasma cells with crystals.

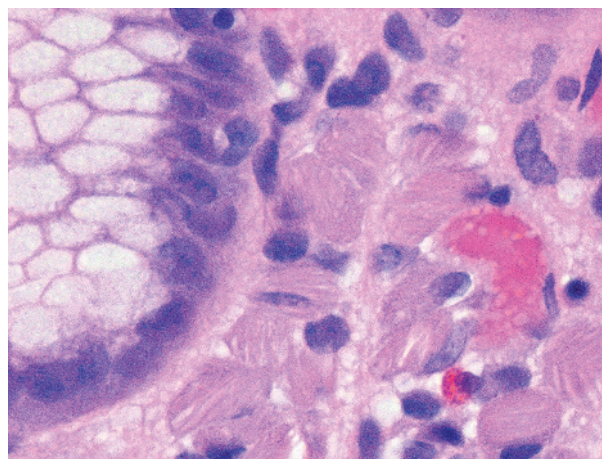
All of the gastric biopsy specimens comprised antral-type mucosa in which there was an acute and chronic gastritis of mild to moderate severity associated with *H. pylori* infection. The mucosal inflammatory component mainly comprised small lymphocytes and morphologically normal plasma cells, but there was also a more focal infiltrate of eosinophil and neutrophil polymorphs. In addition, one of the biopsy fragments from each patient showed plasma cells with abundant pale eosinophilic cytoplasm containing elongated, rectangular or needle-shaped crystalline inclusions (fig 1). The inclusions varied from approximately 5 to 20  $\mu\text{m}$  in length, were non-birefringent and were typically arranged in fan-shaped or parallel arrays. The crystals were not stained with haematoxylin and eosin, Cresyl Violet, Sirius Red or periodic acid-Schiff diastase and therefore appeared as negative images in the cytoplasm of the plasma cells (fig 2). The crystal-containing cells were typically distributed in the superficial perifoveolar lamina propria and were present in variable numbers in the three patients, ranging from 2 to 32/high-power field ( $\times 400$  magnification, field area 0.19  $\text{mm}^2$ ) maximally. In all of the biopsy specimens, morphologically normal plasma cells lacking crystals were much more numerous. No clear relationship was seen between the distribution of the crystal-containing cells and the presence of *H. pylori* organisms or any other associated inflammatory cellular component. Also, there was no evidence of crystal deposition in histiocytes or in extracellular locations. Occasional plasma cells with cytoplasmic Russell bodies were also present, but these inclusions were not observed in the cells with crystals. No histological features were present to suggest gastric lymphoma. None of the biopsy specimens from the other mucosal sites showed plasma cells with crystals.

Immunohistochemistry showed that the morphologically normal plasma cells were polytypic in all cases. Sufficiently numerous crystal-containing plasma cells were present in only two of the biopsy specimens (cases 1 and 3; table 1) to permit immunohistochemical analysis. The crystals themselves were not immunoreactive with any of the antisera tested. However, the cells containing crystals showed CD79a, CD138, IgA and  $\lambda$  light chain expression (figs 3 and 4). The cells with crystals showed no immunoreactivity for cytokeratin, desmin, CD20, CD68, IgG, IgM or  $\kappa$  light chain.

All patients received standard treatment for *Helicobacter* infection with symptomatic improvement and none underwent repeat gastric biopsy. One patient (case 1) died of unrelated causes 4 months after the endoscopy. Serum electrophoresis in this patient did not show an abnormal paraprotein band. The remaining two patients were free from gastrointestinal symptoms 6 and 14 months after biopsy and neither had clinical evidence of lymphoma or myeloma.



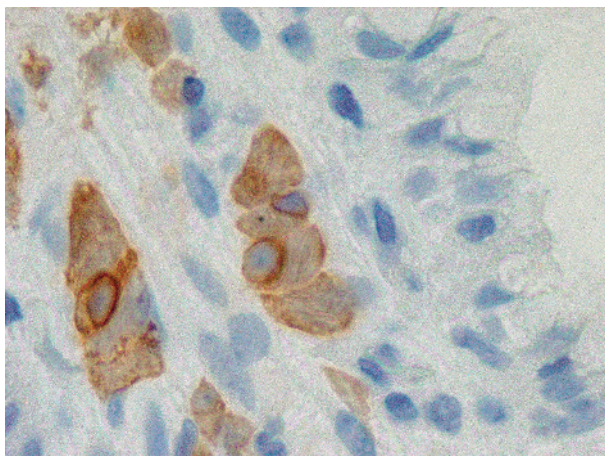
**Figure 1** *Helicobacter*-associated active chronic gastritis. The superficial lamina propria includes plasma cells with abundant eosinophilic cytoplasm.



**Figure 2** Multiple elongated or needle-shaped crystals are evident at high magnification in the cytoplasm of the plasma cells.

## DISCUSSION

The accumulation of intracytoplasmic crystalline inclusions is a rare but well-described feature of B cell lymphoproliferative disorders and is seen most commonly in lymphomas showing plasmacytic differentiation.<sup>1</sup> The formation of crystals in such cases is thought to reflect the altered production, storage or



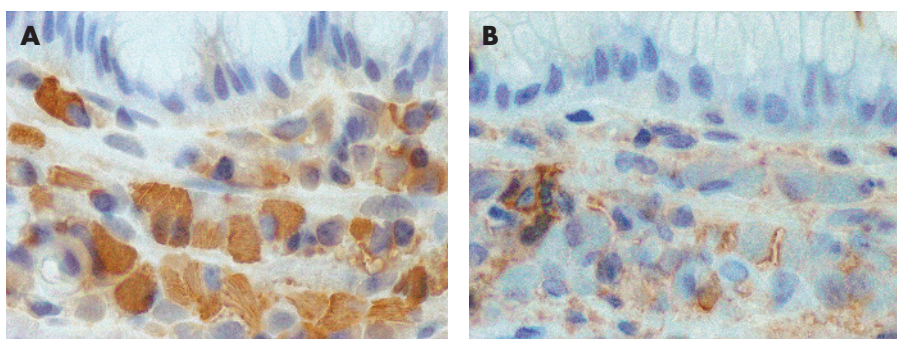
**Figure 3** Immunohistochemistry showing CD79a expression by the cells with cytoplasmic crystals. The crystals are unstained, appearing as "negative" images in the cytoplasm.

secretion of Ig products by the neoplastic cells, and it seems likely that the abnormal proteins exhibit an increased physicochemical tendency to crystallisation. Although the inclusions may be immunoreactive for Ig components, typically there is weak or absent staining. The lack of immunoreactivity may be due to the altered molecular configuration and therefore decreased antigenicity of the stored Ig, or antigen masking resulting from the crystalline structure of the protein.<sup>3 4 12</sup>

Rare reports are available of crystalline inclusions in gastric lymphoproliferative diseases, including three patients with gastric plasmacytoma.<sup>13–15</sup> Crystals were present in the cytoplasm of the neoplastic plasma cells and were also identified in histiocytes in one of the cases.<sup>13</sup> No consistent pattern of Ig heavy chain or light chain expression was present in these tumours. Fend *et al*<sup>16</sup> described an unusual case of gastric mucosa-associated lymphoid tissue lymphoma in a patient who initially presented with a secondary nodal immunoblastic lymphoma. IgG and  $\kappa$  positive crystals were identified in plasma cells in the gastric tumour and more rarely in the immunoblastic tumour component. Interestingly, the patient's initial gastric biopsy specimens had been interpreted as reactive, but on review showed occasional plasma cells with cytoplasmic crystals. In retrospect, the authors considered this finding to indicate involvement by the mucosa-associated lymphoid tissue lymphoma. Other authors have also suggested that the identification of plasma cell crystals can be used to support a diagnosis of lymphoproliferative disorder.<sup>13</sup>

To our knowledge, there is only one previous report of crystals in plasma cells in a patient with gastritis. Erbersdobler *et al*<sup>11</sup> described the case of an 80-year-old woman whose gastric biopsy specimen had a diffuse infiltrate of polytypic plasma cells in the lamina propria, most of which showed prominent eosinophil cytoplasmic inclusions in keeping with "Russell body gastritis". In addition, the authors noted that some plasma cells contained needle-shaped crystalline inclusions similar to those described in this report. *Helicobacter* infection was absent in this patient. Two additional cases of Russell body gastritis have been reported, both in patients with *Helicobacter*-associated gastritis<sup>17 18</sup>; crystals were not documented in these cases. Although Russell bodies were present in our biopsy specimens, they were relatively infrequent and not seen in the cells showing crystalline inclusions. We were able to assess the crystal-containing plasma cells immunohistochemically in two of our patients, and the cells from both showed expression of IgA and  $\lambda$  light chain. The presence of light chain restriction in these patients raises the possibility of a lymphoproliferative process, but there were no histological or endoscopic features to suggest neoplasia, and the more numerous morphologically normal plasma cells in all biopsy specimens were clearly polytypic. Furthermore, no paraprotein was detected on serum electrophoresis in the patient with most numerous crystals, and clinical follow-up was negative in both other patients. We suggest that the immunohistochemical findings most likely indicate the presence of an expanded but reactive clone of plasma cells whose immunoglobulin product was predisposed to crystal formation. Molecular studies have also previously suggested that monoclonal B cell populations are present in some cases of gastritis,<sup>19–21</sup> although the data are conflicting.<sup>22</sup> It is noteworthy that in the two cases in which immunohistological assessment was possible, the crystals were present in plasma cells synthesising  $\lambda$  light chain. Lymphomas with crystalline inclusions also seem to more often express  $\lambda$  light chain.<sup>2</sup> The crystal-containing plasma cell infiltrates in our cases may have been associated with *Helicobacter* infection as crystals were not identified in the biopsy specimens from any of the other mucosal sites. We cannot, however, exclude the possibility that some other localised effect in the gastric mucosa predisposed to crystal deposition.

In conclusion, we described three patients with *Helicobacter*-associated gastritis in whom plasma cells contained intracytoplasmic crystalline Ig inclusions. As crystals were not identified in other mucosal biopsy specimens, it seems that they were possibly related to the *Helicobacter* infection. The presence of such crystals, in isolation, should not be considered proof of a lymphoproliferative process.



**Figure 4** (A) Plasma cells with crystals, showing immunoreactivity for  $\lambda$  light chain. (B) Occasional morphologically normal plasma cells express  $\kappa$  light chain, but the distended crystal-containing cells are not reactive.

## Take-home messages

- Plasma cells with crystalline cytoplasmic inclusions are described in three patients with helicobacter-associated gastritis.
- Immunoglobulin light chain restriction was demonstrated in two of the cases, but there were no clinical or pathological features to suggest neoplasia.
- Crystalline inclusions may be seen within reactive gastric plasmacytic infiltrates and their presence, in isolation, should not be considered indicative of lymphoma.

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